



# Adult-onset Langerhans cell histiocytosis presenting with adipsic diabetes insipidus, diabetes mellitus and hypopituitarism: A case report and review of literature

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## ABSTRACT

Langerhans cell (LCH) histiocytosis occurs in 1 per 560,000 adults with variable manifestations. However, it rarely presents with simultaneous and multiple endocrine dysfunctions early in the course of the disease. We report a case of LCH in an adult manifesting with adipsic diabetes insipidus, diabetes mellitus and hypopituitarism.

A 41-year-old Filipino male presented with polyuria and polydipsia. He was initially diagnosed as a simple case of diabetes mellitus but symptoms did not fully resolve after control of glucose. He had loss of thirst perception, erectile dysfunction and memory impairment. These were followed by crusting skin lesions over the face, trunk and extremities. He was hospitalized because of altered mentation because of severe dehydration, hypernatremia and hyperglycemia. Subsequent work-up showed thickened hypothalamus and infundibulum on magnetic resonance imaging. Skin biopsy and immunostaining with S-100 and CD1a confirmed the diagnosis. There was partial improvement after chemotherapy. He was maintained on desmopressin and testosterone.

Multiple endocrinopathies can be the presenting signs of adult-onset LCH. They can be harbinger of subsequent involvement of other organs. Central diabetes insipidus, other hypothalamic dysfunctions and anterior pituitary hormonal deficiencies, when present at the onset as in this case, will likely have poor response to treatment despite improvement of other non-endocrine organs. The permanent lesions in the hypothalamus and pituitary gland warrants continued endocrine evaluation and intervention.

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## Introduction

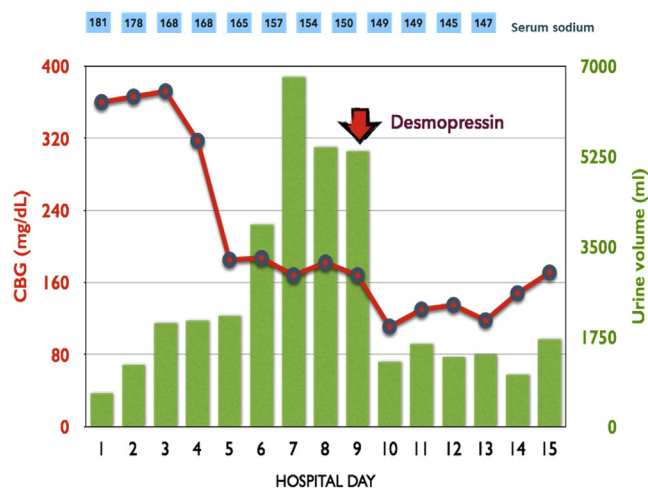
Langerhans cell histiocytosis (LCH) is characterized by proliferation of differentiated cells of the monocyte-macrophage series called histiocytes. It was historically termed as Histiocytosis X and thought to be a reactive disease. Recent data indicate that there could also be an underlying neoplastic mechanism as demonstrated by familial clustering, chromosomal instability and oncogenic BRAF V600E mutation in 57% of cases [1]. It is estimated that 1 case of LCH occurs per 560,000 adult [2,3]. Because the true prevalence and incidence of the disease is low, our current knowledge of its clinical course is mostly based on retrospective data gathered over many years.

The new disease classification has been simplified to single system LCH and multisystem LCH [3]. Multisystem LCH, as seen in 45% of cases, involves 2 or more organs or systems (lung, bone, skin, endocrine and central nervous systems, liver, spleen, lymph nodes and marrow). LCH has a particular predilection for involvement of the hypothalamo-pituitary axis. In a retrospective study by Kaltsas et al. in 2000, he followed 12 adult LCH. DI and anterior pituitary dysfunction were present in 4 and 3 patients respectively but only 1 had both at the onset. None in our literature search and adult patient with LCH presented with both hypothalamus and pituitary dysfunction complicated by adipsia and diabetes mellitus [4].

We report a case of an adult Filipino male diagnosed with LCH and with multiple endocrinopathies, each complicating the other. The central diabetes insipidus was initially masked by diabetes mellitus. Furthermore, the patient was pushed to dehydration by loss of thirst sensation or adipsia. On review of history, he already had manifestation of hypogonadism at the onset of disease. These endocrine dysfunctions heralded other systemic manifestations of

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**Figure 1.** Graphical representation of daily blood glucose levels (red), serum sodium (blue) and urine volume (green). Despite adequate hydration and correction of hyperglycemia, only the introduction of desmopressin had significantly improved serum sodium and urine volume.

the patient. We also gathered current literature on the complex association of these hormonal disorders, the course of the disease and the response to treatment.

### Case report

A 42-year-old Filipino displayed 6-month history of worsening polyuria. He was investigated for diabetes mellitus. The fasting plasma glucose (8.5 mmol/L) and glycosylated hemoglobin (HbA1C, 11%) were elevated hence he was started on insulin and metformin. Glycosylated hemoglobin improved after 3 months to 7.2% however there was still polyuria. Five months later, he noted eruptions of multiple purpuric and pruritic rashes over the trunk and premature loss of teeth. The symptoms were later accompanied by cognitive dysfunction, emotional lability and ataxia. There were also fatigue and loss of libido. Despite persistent polyuria, there was progressive deterioration of thirst perception. He was admitted because of altered mentation secondary to severe dehydration with hypotension (80/50 mm Hg),

tachycardia (138 beats per minute) and azotemia (serum creatinine 194  $\mu$ mol/L and BUN 84 mmol/L). He had hyperosmolar hypernatremia (serum osmolality 360 mOsm/kg/H<sub>2</sub>O; serum sodium 181 mmol/L; plasma glucose 20.2 mmol/L). Despite adequate hydration, there was persistent of hypernatremia and hypoosmolar urine. These and the significant response to desmopressin as depicted in Figure 1 were compatible with complete central DI.

On physical examination was done when he was more stable. He was overweight (body mass index 23.6 kg/m<sup>2</sup>, Asia-Pacific Guidelines). There were multiple pruritic erythematous to purpuric macules and papules with erosions and crusting over the scalp, face and chest. There were also gingival swelling and teeth malocclusion (Figures 2 and 3). He had pallor and gynecomastia. He had no focal motor deficit however he had an ataxic gait.

A cranial magnetic resonance imaging (MRI) on Figure 4 showed thickened hypothalami and pituitary infundibulum. There was also a 6 millimeter pontine lesion. The posterior bright spot was absent. Hormonal tests (shown in Table 1) were consistent with secondary hypogonadism. There was an indirect evidence of growth hormone deficiency. The levels of fasting insulin (35 uIU/mL) and C-peptide (7.33 ng/mL) were elevated. The blood is drawn fasting at 8 in the morning while the patient was off insulin for 5 days. Antibody panel and pancreatic biopsy were not performed. Additional finding were pancytopenia on peripheral blood smear, maxillary-mandibular osteolysis on radiograph and multiple hepatic nodules on computed tomography. Bone marrow biopsy disclosed only moderately hypocellular marrow and erythroid hyperplasia. There were no malignant cells found in the liver biopsy. Punch biopsy of the skin lesions was suggestive of Langerhans cell histiocytosis. Immunostaining for S-100 and CD1a antigens were confirmatory of the diagnosis (Figure 5).

The patient was discharged on desmopressin 0.1 mg twice daily with instruction to drink fixed amount of fluid to avoid wide sodium fluctuations. He was started on testosterone replacement. He received chemotherapy with vinblastine and prednisone for 6 months. There was a significant resolution of skin and gum lesions (Figure 6) and there was improvement in memory, gait and overall function. A repeat cranial MRI demonstrated no difference from pre-treatment findings, consistent with the refractory status of the DI and anterior pituitary hormone deficiencies. He was still maintained on insulin for the diabetes mellitus.



**Figure 2.** Multiple purpuric rashes over the scalp, face and chest.

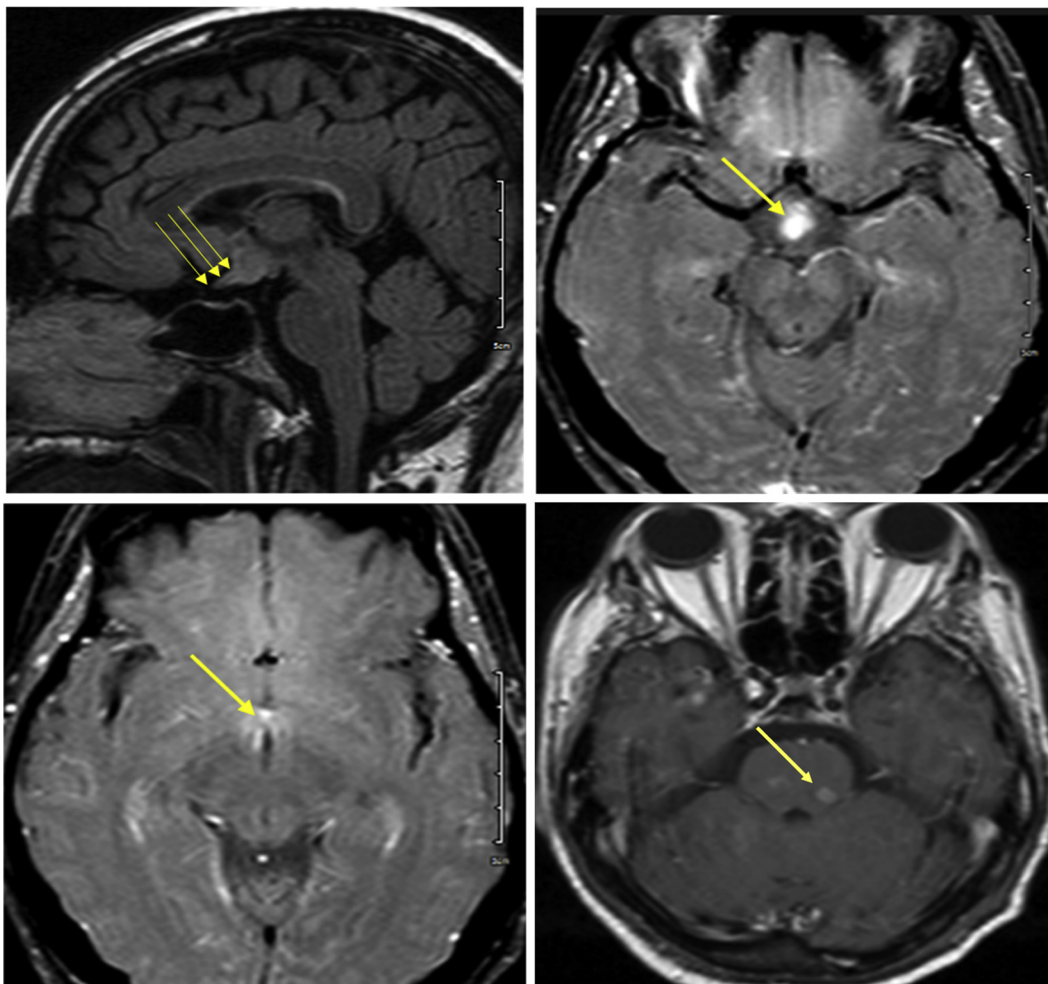


**Figure 3.** Gingival swelling (left) and accelerated loss of teeth with osteolytic lesions of the alveolar bone on radiograph (right).

## Discussion

Endocrinologists should consider LCH in an adult patient presenting with DI and anterior pituitary hormone deficiency on the background of sellar or parasellar lesions. MRI would show loss of pituitary bright spot, thickened infundibulum and hypothalamic enhancement as noted in this patient. Other neoplastic, inflammatory or infectious and infiltrative diseases need to be ruled out. In a registry report of 274 adults with biopsy-proven adult LCH, there was a slight male preponderance (52.2%) and the mean age at the onset of diagnosis was  $33 \pm 14$  years; 68.6% had multisystem disease and 29.6% had diabetes insipidus [2].

Central DI can develop either before, simultaneous with or subsequent to a diagnosis of LCH based from the presence of other lesions. Among pediatric patients, multisystem disease and craniofacial involvement at diagnosis carry a significantly increased risk to develop DI during their course [5]. On the other hand, DI can be the presenting feature in about 1/3 of patients [4]. It has been reported that pituitary stalk thickening precedes peripheral lesions by several months. During this early phase of the disease, a water deprivation test and possibly pituitary stalk biopsy may be helpful. In 2 studies evaluating the efficacy of chemotherapy among children with LCH, pre-existing central DI were neither reversed nor ameliorated by chemotherapy. On the other hand, 2 cases of partial



**Figure 4.** Cranial MRI showing thickened pituitary infundibulum (upper left panel); contrast enhancement of the infundibulum (upper right panel) and hypothalamus (lower left panel); and a 6-mm pontine lesion (lower right panel).



**Table 1**  
Biochemical endocrine tests<sup>a</sup>

	Result	Reference
Serum TSH	1.5 uIU/mL	0.4–4.5
Serum free T4	1.6 ng/dL	0.8–1.8
Serum cortisol	17.8 mcg/dL	5–25
Serum FSH	2.82 mIU/mL	1–8
Serum LH	2.38 mIU/mL	1.14–8.75
Serum testosterone	0.84 ng/mL	1.95–11.38
Serum prolactin	8.6 ng/mL	4–23
Serum IGF-1	62 ng/mL	121–237
Plasma glucose	6.8 mmol/L	3.6–5.6
Plasma insulin	35.0 uU/mL	5–10
Plasma C-peptide	7.33 ng/mL	0.78–5.19

<sup>a</sup> The blood is drawn fasting at 8 in the morning. The plasma insulin and C-peptide was taken while the patient is off insulin for 5 days.

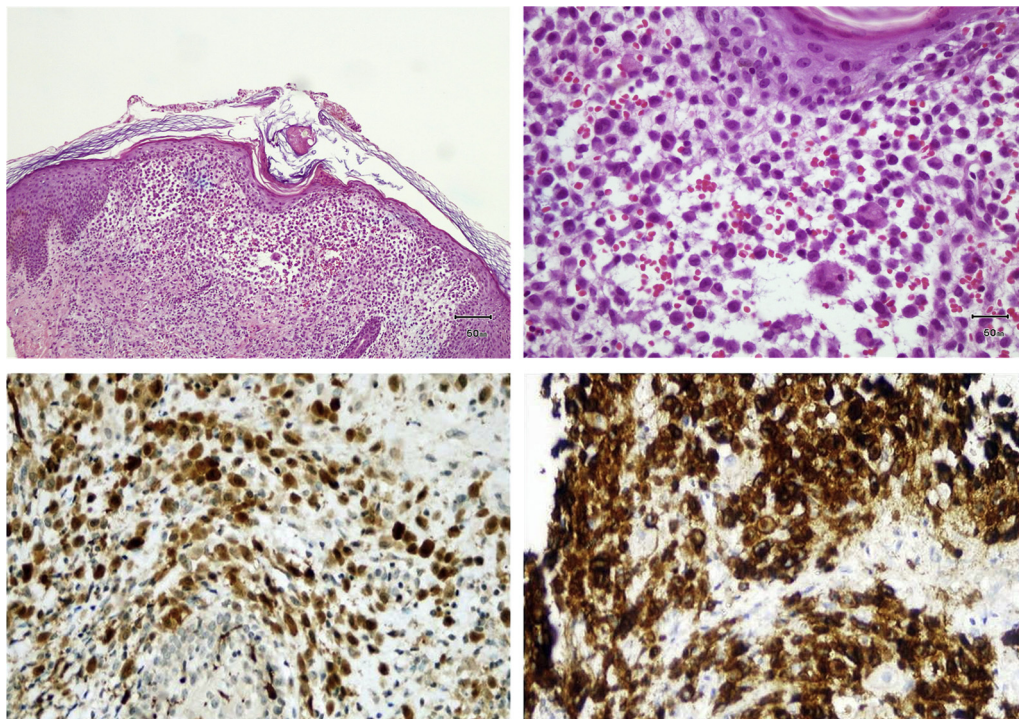
central DI undergo complete remission after chemotherapy with discontinuation of desmopressin and disappearance of pituitary stalk thickening [6,7]. There is one case report of successful treatment after chemotherapy with vinblastine, prednisolone and 6-mercaptopurine [8]. However, most central DI in adult multisystem LCH were advanced at the time of therapy. Adipsic hypernatremia was reported after surgical clipping of aneurysm or excision of large craniopharyngioma and macroadenoma [9]. There was one report of adipsic diabetes insipidus in LCH. The probable mechanism behind adipsic hypernatremia in LCH could be infiltration of thirst center osmoreceptors in the hypothalamus. In a retrospective review of 12 patients with LCH and DI by Kaltsas et al., 8 eventually developed anterior pituitary hormone deficiencies at a median of 4.5 years (range 2–22). In the same study, the most common and earliest hormone deficiency was growth hormone (median 2 years, range 2–22) followed by FSH-LH (median 7 years, range 2–22). TSH and ACTH deficiencies were noted after a median of 10 years.

Prolactin elevation, if present, is attributable to hypothalamic infundibular infiltration wherein there is impaired release of inhibitory dopamine.

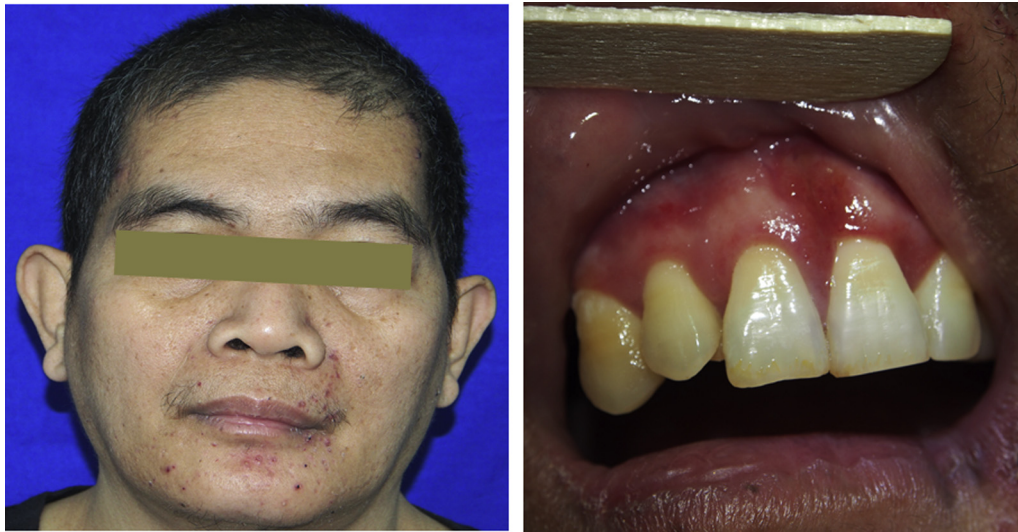
Nonendocrine hypothalamic dysfunctions like adipsia and memory impairment may follow. It is usually seen at a median of 10 years [4]. The lack of thirst perception and noncompliance due to memory disturbance would have significant impact among patients with LCH and DI. Weight, sleep and thermoregulatory disorders are also possible. The varying presentation and their timing of manifestation reflect the heterogenous nature of the disease. The structural changes in the hypothalamic-pituitary axis often heralds involvement of the other parts of the central nervous system and its attendant neurologic sequelae which probably reflects the progressive and permanent nature of this infiltrative disease. Effective measures that can prevent or reverse neuroendocrine deterioration remain to be defined.

It is very interesting to know whether diabetes mellitus is part of histiocyte infiltration of pancreatic  $\beta$ -cells or a result of obesity and insulin resistance secondary hypothalamic involvement. In an observational study by Alexandraki et al., 4 out of 14 patients with LCH had abnormal glucose metabolism (3 impaired glucose tolerance and 1 diabetes mellitus). This abnormality in glucose metabolism, observed only in active disease, was attributed to pro-inflammatory state [10]. To date, only one study reported pancreatic infiltration but this was a child and not associated with diabetes mellitus [11]. In the case presented, the clinical features and biochemical tests favored type 2 DM (overweight and insulin resistance). Autoimmune panel may help but only pancreatic biopsy can give the definitive diagnosis.

The treatment of multisystem LCH conventionally follows those of pediatric cases. A combination of vinblastine and prednisone is given in the initial (6 weeks) and maintenance (12 months) phase [12]. Lack of response after 6 months of treatment is associated with treatment failure and high (66%) mortality [13].



**Figure 5.** Skin punch biopsy showing characteristic LC infiltrates with reniform nuclei and nuclear groove (H&E, upper panel) and positive immunostaining for S100 (lower left panel) and CD1a (lower right panel).



**Figure 6.** Improvement of skin and gum lesions 6 months after the patient received his initial dose of vinblastine and prednisone chemotherapy.

Some centers recommend cytarabine or cladribine as first line drug for multisystem LCH with lung or bone lesion [14,15]. Vemurafenib, a novel tyrosine kinase inhibitor, is a targeted therapy for refractory LCH [16]. The mainstay of treatment in adipic DI associated with LCH is desmopressin, a synthetic long-acting vasopressin analog, together with fixed fluid intake. Testosterone is beneficial for symptoms of hypogonadism as well as anemia. Growth hormone deficiency in adults needs to be addressed. Anticipation of secondary hypothyroidism and adrenal insufficiency is part of the disease monitoring.

## Conclusion

To the best of our knowledge, this is the first case of adult-onset Langerhans cell histiocytosis presenting simultaneously with multiple endocrinopathies at the onset of the disease. In this case, the presence of complete central DI with adiposia and hypopituitarism in conjunction with structural abnormalities seen in MRI at diagnosis portends poor response of these endocrine organs to chemotherapy. Diabetes mellitus may complicate the early diagnosis of central DI which is said to have better prognosis when diagnosed earlier. The onset of anterior pituitary hormone deficiencies cannot be predicted in LCH. Hence, regular endocrine monitoring should be implemented.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

## Conflict of interest

The authors declare they have no conflicts of interest.

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